Complete Summary

GUIDELINE TITLE

Management of type 2 diabetes mellitus.

BIBLIOGRAPHIC SOURCE(S)

University of Michigan Health System. Management of type 2 diabetes mellitus. Ann Arbor (MI): University of Michigan Health System; 2008 Jan. 21 p. [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: University of Michigan Health System. Management of type 2 diabetes mellitus. Ann Arbor (MI): University of Michigan Health System; 2007 Jul. 20 p. [15 references]

The University of Michigan Health System updated this guideline to include information on exenatide (Byetta), dipeptidyl peptidase-4, and Exubera that was released after the publication of the July 2007 version of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- February 26, 2008, Avandia (rosiglitazone): A new Medication Guide for Avandia must be provided with each prescription that is dispensed due to the U.S. Food and Drug Administration's (FDA's) determination that this medication could pose a serious and significant public health concern.
- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- November 14, 2007, Avandia (rosiglitazone): New information has been added to the existing boxed warning in Avandia's prescribing information about potential increased risk for heart attacks.
- October 16, 2007, Byetta (exenatide): Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.
- August 14, 2007, Thiazolidinedione class of antidiabetic drugs: Addition of a boxed warning to the updated label of the entire thiazolidinedione class of antidiabetic drugs to warn of the risks of heart failure.

- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Type 2 diabetes mellitus

GUIDELINE CATEGORY

Diagnosis
Management
Prevention
Screening
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Geriatrics
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To improve adherence to important, morbidity-reducing recommendations for preventing, detecting, and managing diabetic complications

TARGET POPULATION

Adults seen in primary care settings including those at risk for or diagnosed with diabetes mellitus

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Fasting glucose
2. Oral glucose tolerance test (OGTT)

Screening/Prevention/Treatment/Management

Hypertension

1. Monitor blood pressure, electrolytes, serum creatinine
2. Treatment: thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers
3. DASH diet and exercise

Glycemic Control

1. Monitor glycated hemoglobin (HbA1c)
2. Pharmacologic management
    - Oral agents (metformin, sulfonylureas, thiazolidinediones)
    - Insulin agents (NPH, detemir, glargine, premixed)
    - Other (exenatide)

Lipid Control

1. Monitor lipid profile
2. Treatment with statin

Cardiovascular Risk Reduction

1. Check smoking status and encourage cessation
2. Aspirin therapy

Other Ongoing Screening and Management

1. Weight
2. Feet inspection
3. Review of self-management goals
4. Retinal examination and treatment of retinopathy
5. Screening for microalbuminuria and treatment with ACE inhibitor or ARB

6. Serum creatinine and estimated glomerular filtration rate (eGFR)
7. Monofilament testing of feet
8. Preconception counseling and pregnancy
9. Consultation or referral for special circumstances

MAJOR OUTCOMES CONSIDERED

- Progression from impaired glucose tolerance (IGT) to diabetes
- Glycemic control, based on percent hemoglobin A1c or glycosylated hemoglobin
- Incidence of cardiovascular and microvascular disease (including retinopathy, nephropathy, and neuropathy)
- Incidence of end-stage outcomes of diabetes including blindness, renal failure, and amputation
- Mortality rate among patient with diabetes
- Cost of medical care
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search for this update began with the results of the literature searches performed for the previous updates of this guideline. When recent evidence reviews were not available for a topic, new searches of primary literature were performed. For these topics literature searches were conducted on Medline in February 2003. The searches were performed prospectively using the major key words of diabetes mellitus; consensus development conferences, practice guidelines, guidelines, outcomes and process assessment (health care); clinical trials, controlled clinical trials, multicenter studies; English language; and published from 1995 to present. Terms for specific topic searches within the major key words included: alpha-glucosidase inhibitors, thiazolidinediones, nonsulfonyluric secretagogues (repaglinide, nateglinide), new insulins (glargine, aspart, lispro); chromium, nephropathy (screening, treatment), and neuropathy (screening and treatment).

The search was conducted in components each keyed to a specific causal link in a formal problem structure. The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was single cycle.

Team members then identified major evidence searches and major clinical trials performed since that time. The evidence summary and clinical practice recommendations of the American Diabetes Association (ADA) [2004] were the basis for screening recommendations. The topic of impaired fasting glucose

tolerance ("pre-diabetes") was already addressed in a recent literature search and publication by one of the team members. Glycemic control was based on the United Kingdom Prospective Diabetes Study (UKPDS) for control value and the American Diabetes Association (ADA) recommendations for goal. Life style modifications (diet, exercise) were based on the UKPDS and Diabetes Prevention Program (DPP) studies. Comments about treatment for type 1 diabetes and insulin use are based on the Diabetes Control and Complications Trial (DCCT). Treatment for type 2 diabetes with sulfonylureas and metformin is based on the UKPDS. Screening and treatment of hypertension and lipid levels in type 2 diabetes is based on an evidence review and recommendations performed by the American College of Physicians, which included a member of our team. Screening and treatment for retinopathy were based on a literature review performed by the U. S. Veterans Administration. Recent evidence reviews were not available for the remaining topics.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence for the Most Significant Recommendations

A. Randomized controlled trials
B. Controlled trials, no randomization
C. Observational trials
D. Opinion of expert panel

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data. If randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developer reviewed cost analyses.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Drug tables were reviewed by UMHHC Pharmacy Services. The guideline was reviewed at clinical conferences or grand rounds meetings of divisions and departments to which the content is most relevant. This guideline was reviewed at meetings of, Family Medicine; General Medicine; and Metabolism, Endricinology, and Diabetes. The revised document is reviewed by the Guidelines Steering Committee, composed of representatives from all primary care specialties. The UMHS Executive Committee on Clinical Affairs performs a final review prior to institutionally endorsing the guideline.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The following key points summarize the content of the guideline. Refer to the full text for additional information, including dosing and cost considerations for oral agents for the management of type 2 diabetes and self-management topics. The levels of evidence [A–D] are defined at the end of the "Major Recommendations" field.

Screening

Although little evidence is available on screening for diabetes, one may consider beginning screening at age 45 at 3–year intervals, earlier particularly if body mass index (BMI) $\geq$25 kg/m^2 [*D*].

Prevention

In individuals at risk for diabetes (see Table 1 in original guideline document), diet, exercise, and pharmacologic interventions can delay or prevent type 2 diabetes [*A*].

Diagnosis

Either two separate fasting glucoses ≥126 mg/dL, or if symptoms, a glucose ≥200 mg/dL confirmed on a separate day by a fasting glucose ≥126 mg/dL, or 2-hour postload glucose ≥ 200 mg/dL during an oral glucose tolerance test [*B*]. (See Table 1 in the original guideline document.) Glycated hemoglobin (HbA1c) has low sensitivity, but high specificity, for the diagnosis of diabetes, and most experts feel that it should not be used as a primary diagnostic test.

Treatment

Diet, exercise, and pharmacologic interventions should be initiated for:

- Hypertension control [*A*]
- Glycemic control [A]
- Lipid control [*A*]
- Cardiovascular risk reduction [*A*]

Ongoing Screening and Management

Routine screening and prevention efforts for cardiovascular risk factors (hypertension, hyperlipidemia, tobacco use) and for microvascular disease (retinopathy, nephropathy, neuropathy) are recommended to be performed in the following time frames. (See the original guideline document for management of risk factors, complications, and glycemia.)

Each Regular Diabetes Visit	Every 3 to 6 Months	Annually (see Table 2 in the original guideline document)
• Diabetes visit every 3 months for patients on insulin; every 6 months for patients on oral agents or diet only [*D*] • Blood pressure measured and controlled [*A*] (see Table 2 in the original guideline document) • Weight checked [*D*] • Inspect feet each visit if presence of neuropathy; otherwise annually [*A*] (see Tables 2 and 8 in the original guideline document) • Smoking cessation counseling	• Check HbA1c and optimize glycemic control [*A*] (see Table 4 in the original guideline document)	• Dilated retinal examination by an eye care specialist [*B*] and treatment of retinopathy [*A*] (Biannually if previous eye exam was normal, see Table 2 in the original guideline document) • Screen for microalbuminuria if not on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ARB) [*B*]. Prescribe an ACE-1 or ARB for microalbuminuria or proteinuria [*A*] • Serum creatinine and estimated glomerular filtration rate (eGRF) [*D*]. • Monofilament testing of feet [*A*] (see Table 9 in the original guideline document) • Lipids measured [*B*] and treated [*A*] (see Table 2 in the original guideline document)

Each Regular Diabetes Visit	Every 3 to 6 Months	Annually (see Table 2 in the original guideline document)
provided for patients with tobacco dependence [*B*] (see Table 2 in the original guideline document) • Very important self-management goals reviewed and reinforced [*A*] (see Table 8 in the original guideline document)		• Smoking status assessed • Other important self-management goals reviewed and reinforced (see Table 8 in the original guideline document)

Special considerations: Pregnancy. Preconception counseling and glycemic control in women with diabetes mellitus results in optimal maternal and fetal outcomes [*B*].

Definitions:

Levels of Evidence

A. Randomized controlled trials
B. Controlled trials, no randomization
C. Observational trials
D. Opinion of expert panel

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and graded for the most significant recommendations (see "Major Recommendations").

Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data. If randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriated management of type 2 diabetes and diabetic complications
- Reduced morbidity from type 2 diabetes mellitus

POTENTIAL HARMS

Side Effects of Medications

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs can reduce the efficacy of angiotensin-converting enzyme (ACE) inhibitors, may lead to increased blood pressure, may be associated with increased cardiovascular events, and can precipitate acute renal failure in patients with impaired renal function. Some NSAIDs may also interfere with the anti-platelet activity of aspirin.

Antihypertensive Agents

- High-dose thiazide diuretics have been reported to have a variety of adverse effects including worsening of hyperlipidemia, deterioration of glycemic control, impotence, and increased mortality, so thiazides should be used at low doses.
- Angiotensin-converting enzyme (ACE) inhibitors can lead to cough; ACE inhibitors and angiotensin II receptor antagonists (ARBs) can lead to renal insufficiency, and hyperkalemia; careful monitoring of serum electrolytes is therefore warranted with these agents.
- Beta-blockers may decrease high density lipoprotein (HDL) and increase triglyceride levels, and in one major trial, beta-blockers were more frequently discontinued and led to more weight gain and higher doses of glucose-lowering agents than ACE inhibitors. If a beta-blocker is used, it should be cardioselective.

Oral Hypoglycemic Agents

- Gastrointestinal side effects, including diarrhea, are seen in up to 30% of patients using metformin.
- Gastrointestinal side effects including abdominal pain, flatulence, and diarrhea are common with alpha-glucosidase inhibitors. These effects usually diminish over time (4–8 weeks), buy frequently lead to discontinuation of the drug.
- There is a possible increased risk of myocardial infarction with rosiglitazone.
- Thiazolidinediones are associated with fluid retention and peripheral edema, which occur in at least 15% of patients. Thiazolidinediones have been noted to worsen diabetic macular edema.
- The most common side effects of Byetta are nausea and vomiting. The U.S. Food and Drug Administration warns that Byetta may be associated with an increased risk for pancreatitis.
- Symlin is used at mealtimes to augment the effects of insulin on glycemic control. This can cause severe hypoglycemia which can occur within 3 hours

after a symlin injection. Symlin and insulin should never be mixed. Nausea is the most common side effect but improves with time in most patients.

Other Potential Harms

Risk of tight control: The major risk of intensive glycemic control is hypoglycemia.

Individuals with the following characteristics are at heightened risk with tight glycemic control:

- History of severe hypoglycemia (inability to treat without assistance): any episodes within the past year and/or more than 2 episodes ever
- Hypoglycemia unawareness
- Advanced cardiovascular or cerebrovascular disease
- Autonomic neuropathy (especially cardiac)
- Comorbidities/medications that impair the detection of hypoglycemia (e.g., central nervous system [CNS]-acting drugs, alteration in mental status)
- Lack of mobility or lives alone

CONTRAINDICATIONS

CONTRAINDICATIONS

- Hypersensitivity reactions and angioedema are contraindications to angiotensin-converting enzyme (ACE) inhibitor therapy for hypertension.
- Some members of the dihydropteridine class of calcium channel blockers may increase urinary albumin excretion and should be avoided in patients with microalbuminuria.
- Metformin should be avoided in patients with reduced creatinine clearance or at risk for acidosis (e.g. cirrhosis or congestive heart failure [CHF]).
- The U.S. Food and Drug Administration has issued a black box warning for thiazolidinediones due to an increased risk of CHF; therefore these drugs should be avoided in patients with significant CHF.

QUALIFYING STATEMENTS

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

This guideline was partially adapted as follows:

- Screening and glycemic goal recommendations were based on "American Diabetes Association. Clinical practice recommendations 2004. Diabetes Care. 2004;27(Suppl 1):S1-S140."
- Screening and treatment of hypertension and lipid levels in type 2 diabetes recommendations are based on "Lipid control in the management of type 2 diabetes mellitus: A Clinical Practice Guideline from the American College of Physicians, Clinical Efficacy Assessment Subcommittee (2004)."

DATE RELEASED

1996 May (revised 2008 Jan)

GUIDELINE DEVELOPER(S)

University of Michigan Health System - Academic Institution

SOURCE(S) OF FUNDING

University of Michigan Health System

GUIDELINE COMMITTEE

Diabetes Mellitus Guideline Team

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Team Leaders: Sandeep Vijan, MD, General Internal Medicine

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member/Relationship/Company

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GUIDELINE AVAILABILITY

Electronic copies: Available for download in Portable Document Format (PDF) from the University of Michigan Health System Web site.

AVAILABILITY OF COMPANION DOCUMENTS

Continuing Medical Education (CME) information is available from the University of Michigan Health System Web site.

PATIENT RESOURCES

Several patient education resources about diabetes are available from the University of Michigan Health System Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on May 20, 1999. The information was verified by the guideline developer on June 17, 1999. This NGC summary was updated by ECRI on October 12, 2004. The updated information was verified by the guideline developer on October 22, 2004. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on January 11, 2006 following the U.S. Food and Drug Administration advisory on rosiglitazone. This summary was updated by ECRI Institute on September 5, 2007 following the U.S. Food and Drug Administration advisory on the Thiazolidinedione class of antidiabetic drugs. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This NGC summary was updated by ECRI Institute on January 23, 2008. The information

was verified by the guideline developer on February 11, 2008. This summary was updated by ECRI Institute on March 10, 2008 following the U.S. Food and Drug Administration advisory on Avandia (rosiglitazone maleate).

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